Protocol for a systematic review and network meta-analysis of the use of prophylactic antibiotics in hand trauma surgery

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Abstract

Background: The use of prophylactic antibiotics in surgery is contentious. With the rise in antimicrobial resistance, evidence based antibiotic use should be followed. This systematic review and network meta-analysis will assess the effectiveness of different antibiotics on the prevention of surgical site infection (SSI) following hand trauma surgery.

Methods and analysis: The databases EMBASE, MEDLINE, CINAHL and CENTRAL, metaRegister of controlled trials, clinicaltrials.gov and the WHO International Clinical Trials Registry Platform will be searched for published and unpublished studies which will then be screened by two persons independently to identify eligible studies.

This systematic review will include both randomised and non-randomised prospective comparative studies in participants with hand and/or wrist injuries requiring surgery. The network meta-analysis will compare the use of different prophylactic antibiotics against each other, placebo and/or no antibiotics on the development of SSI within 30 days of surgery (or 90 days if there is an implanted device).

The Cochrane Risk of Bias tool 2 will be used to assess the risk of methodological bias in randomised controlled trials and the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool will be used to assess the risk of bias in non-randomised studies. The ROB-MEN tool will be used to evaluate the risk of bias due to missing evidence in network meta-analysis.

A random effects network meta-analysis will be conducted along with subgroup analyses looking at antibiotic timing, operation type and injury type. Sensitivity analyses including only low risk of bias studies and the study location will be conducted and the confidence in the results will be assessed using Confidence in Network Meta-Analysis (CINEMA).

Discussion: This systematic review and network meta-analysis aims to provide an up to date synthesis of the studies assessing the use of antibiotics following hand and wrist trauma to enable evidence-based peri-operative prescribing.

Registration: Prospero registration number CRD42023429618

Background

Hand injuries account for approximately 20% of the UK's Accident and Emergency attendances (1) and its incidence is increasing (2). Not only do hand injuries present a significant burden to the health system, their influence on a patient's work capacity and daily activities present an additional economic impact (3). This impact is compounded by complications after hand surgery, including surgical site infections (SSI), resulting in loss of function and stiffness (4, 5). Previous literature shows that the risk of SSI after hand trauma surgery is at least 5–10%, but this may be even higher (6, 7). Although numerous interventions exist to reduce SSI risk in surgery, few have been tested in randomised controlled trials (RCTs) in hand trauma. Systemic antibiotics are widely used in hand surgery to minimise infectious

surgical complications and subsequent morbidity (8). However, with the rise in global antimicrobial resistance the efficacy of prophylactic antibiotics should be evaluated to support the judicious use of antibiotics.

A variety of studies have shown the lack of efficacy of prophylactic antibiotic in elective hand surgeries (9). Since then, further prospective cohort studies have been published by Kistler et al., (10) and Backer et al., (11) looking at 377 and 434 patients respectively undergoing elective hand surgery and again showing no benefit of prophylactic antibiotics in elective hand surgery. The use of prophylactic antibiotics in traumatic hand surgery was explored by Murphy et al., (2016), in patients undergoing surgery for simple hand surgeries (12) and again they showed no therapeutic benefit of prophylactic antibiotic in reducing the risk of SSI (RR 0.89, 95% CI 0.65–1.23; restricting to 5 double blind RCTs RR 0.66, CI 0.36–1.21). Both analyses yielded wide 95% confidence intervals meaning that there is residual uncertainty.

In the proposed network meta-analysis (NMA), we will pool all prospective comparative studies to assess the efficacy of different classes of antibiotics, no antibiotics and placebo in their prevention of post-surgery SSI for hand and wrist injuries. As NMAs assess both direct and indirect evidence, they have several distinct advantages over standard (pairwise) meta-analyses, including better precision and power (13), the ability to compare interventions that have not been directly compared before (i.e. in a real-life head-to-head study), and the capacity to rank competing treatments to inform clinical decisions (14). This may enable us to generate robust evidence to form the basis of guidelines and inform the future direction of research in relationship to antibiotic use in hand and wrist surgery.

Method and analysis

This NMA will follow the PRISMA guidelines extension for NMA (see additional file 1) (15). This protocol has been registered with PROSERO (ID CRD42023429618). The report in PROSPERO will be updated with any required amendments.

Characteristics of studies

All prospective comparative studies comparing active antibiotics, or to placebo or no antibiotic in patients undergoing surgery following hand and/or wrist trauma will be included. Both randomised and non-randomised trials will be included.

Characteristics of participants

Participants of all ages undergoing hand and or wrist surgery for traumatic injuries within two weeks of their injury will be included. Participants with elective operations will be excluded. There will be no restrictions in terms of gender, ethnicity, comorbidities, mode of injury, contamination status, injury severity and time of presentation.

Interventions

All antibiotics in oral or injectable form used within its licensed therapeutic dosages will be included. Antibiotics will be grouped based on their classes i.e. macrolides, penicillins, cephalosporins reflecting their mechanism of action. Both oral, IM and IV forms will be grouped together due to their common short acting nature. Placebo and no antibiotic use will be grouped due to the anticipated lack of placebo effect on SSI development. It has been hypothesised that antibiotics should be given 30-60 minutes before surgery to allow tissue concentration to reach therapeutic levels at the time of operation. (16) We will thereby assess the effect of the timing of antibiotic use (pre-, intra-, post-operative) with further subgroup analyses.

Outcome measures

The primary outcome investigated will be a dichotomous outcome assessing the development of surgical site infection within 30 days of the operation or within 90 days if a prosthetic material is implanted (as defined by the CDC). (17) SSI diagnosis by any method will be included and its definition outlined in a descriptive table.

Search strategy and study selection

The electronic databases EMBASE, MEDLINE, CINAHL and CENTRAL will be searched for published comparative studies. The electronic search will be supplemented by a manual search for unpublished and ongoing comparative studies in the metaRegister of controlled trials, clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished data to reduce publication and reporting bias. We will use CitationChaser to perform forward and backwards citation chasing (18). We will include all studies irrespective of their country of origin or language. Two persons will independently review references and abstracts retrieved by the search to identify eligible studies. Disagreements will be resolved via a discussion with a third member and a study attrition chart will be used to present the outcomes of the search strategy and subsequent screening process.

Data extraction

Data will be extracted from the eligible studies and cross-checked for data discrepancies by a second reviewer. Information extracted will include:

- General study characteristics (e.g. author, publication year, study type)
- Methodology information (e.g. duration, blinding, randomisation, SSI criteria)
- Participant characteristics (e.g. age, co-morbidities, gender)
- Injury characteristics (e.g. type of injury, operation performed)
- Antibiotic characteristics (dose, mode, type, timing of use)
- Outcome measures

The dichotomous primary outcome of SSI will be recorded in the outcome measures section descriptively and as a proportion of overall study population. As symptoms of SSIs typically occur 3-7

days post-surgery (19) follow up in the acute period post-surgery will be deemed sufficient and complete follow up to 30 days (or 90 days in implanted devices) will not be required. Loss to follow up can be due to a lack of post-operative complication or follow up and treatment in community setting thereby causing difficulty in the interpretation of missing data. Outcomes of patients who do not attend follow up or leave the study early will thus be excluded from the study via a per protocol analysis.

We anticipate a high variability of definition and determination of SSI as this is a subjective outcome which will be dependent on factors such whether this is reported by a clinician or self-reported by the patient or whether an in-person clinical examination is conducted compared to telephone questionnaires. There will also be variability on other wound management techniques such as irrigation and anti-septic cleaning. These details will be collated from the papers published and presented in a descriptive table.

Risk of bias assessment

The risk of bias will be evaluated in the following domains: allocation sequence, allocation concealment, blinding of participants and study personnel, blinding of outcome assessment attrition, selective reporting and other domains including sponsorship bias. The risk of bias of RCTs will be assessed using the Cochrane ROB-2 tool (20) and non-randomised studies will be assessed with the ROBIN-I tool (21). The risk of bias due to missing evidence will be assessed using the ROB-MEN tool (22). A random 20% of studies will be checked independently by a second reviewer for consistencies.

Data analysis

Transitivity is the fundamental assumption of NMAs and will be investigated carefully as treatments cannot be jointly analysed if the network is intransitive (23). We assume that patients who fulfil the inclusion criteria are equally likely to receive any of the antibiotic treatments we are planning to compare. Clinical characteristics which have not been shown to affect infection development in hand surgery include location of operation (24), time to surgery (25), depth and extent of injury (26) and diabetes (9). We will investigate age, injury location and type with regards to its distribution between the studies. If the collected studies appear to be sufficiently similar with respect to the distribution of effect modifiers we will proceed to NMA.

We will produce a network plot to summarise the interventions followed by a series of frequentist, random-effects NMAs using the netmeta package in R assuming a single heterogeneity parameter (27).

To assess the agreement between randomised and non-randomised studies, we will perform separate NMAs and compare the results (28). This will be supplemented by a series of “designed-adjusted analyses”, whereby data from randomised studies will be combined with down-weighted data from non-randomised studies (NRS) using the following variance inflation factors: w=1 (corresponding to the naïve NMA, i.e. all studies at face value), 0.8, 0.6, 0.4, 0.2 and 0 (i.e. zero excludes NRS). These will be displayed as forest-plots per treatments against the reference. If no discrepancies are observed in any of

these analyses, we will proceed to joint (“naïve”) analysis pooling both randomised and non-randomised data as the primary analysis.

Interventions will be ranked by their P-scores using the netrank function; P-scores are assumed to take a value between 0 and 1, with a higher score indicating a better treatment (29). With the netleague package, we will generate league tables with the intervention efficacy ordered by P-score. Forest plots of relative risks (RR) and 95% confidence intervals (CI) will be generated with placebo as the reference treatment. Heterogeneity will be quantified through the standard deviation of random effects (τ, assumed common for all comparisons). To assess inconsistency, we will use both global and local methods with the netsplit package (30), (31) and display the findings via heat plots using the netheat command (32). In case of inconsistency we will investigate for possible sources and if appropriate, further explored by network meta-regression and subgroup analyses.

Given that SSI is rare, we will perform sensitivity fixed-effects Mantel-Haenszel NMA (33) using the *netmetabin* package and inconsistency will be assessed using the *netsplit* package and SIDDE approach.

Network meta-regressions or subgroup analyses will be used to investigate the impact of (a) injury type (b) operation type (c) antibiotic timing. There will likely be heterogeneity and inconsistency due to the wide range of study settings and the relatively small sample size. We anticipate that there may be heterogeneity resulting from differing bacterial flora on the hand due to the location of the study, thereby affecting bacterial susceptibility profiles. Thus the sensitivity of the conclusion will be evaluated by analysing studies at low risk of bias and the location of the study.

We will explore the confidence in estimates of the conclusion with be evaluated with the Confidence in networked meta-analysis (CINeMA) framework which considers the six domains within-study bias, reporting bias, indirectness, heterogeneity, incoherence and imprecision (34).

To estimate the overall prevalence of SSI, we will use the R package metaprop (35) with Hartung-Knapp-Sidik-Jonkman random-effects and the Freeman-Tukey double arcsine transformation to stabilise the variances.

The relationship between study size and effect size (also known as small study effects) will be explored with a comparison-adjusted funnel plot.

Discussion

Current NICE guidelines recommend prophylactic antibiotics for clean surgery involving the placement of a prosthesis or implant, clean-contaminated surgery, contaminated surgery and surgery on a dirty or infected wound. (36) No specific guidelines are provided for hand trauma leading to a wide variation in antibiotic use in clinical practice.

Although the meta-analysis published in 2016 (12) showed no difference in the use of antibiotics in preventing SSIs in simple hand injuries, the paper was limited by the number of high quality studies and the result was concluded via pooled RCT and cohort study results. On closer inspection of the result, the pooled risk ratio was 0.89 with a wide 95% CI 0.65–1.23. In addition, the result of the studies with lower risk of biases Whittaker et al., and Berwald et al., both also have a risk ratio of 0.61 and 0.17 with wide confidence intervals.

Studies assessing complex hand injuries such as fractures and crush injuries present mixed conclusions regarding antibiotic use. Ketonis et al., published a systematic review in 2017 looking at SSIs in open fractures of the hand and concluded the use of antibiotics associating with lower odds of infection. (37) However, the double blind RCT included within the review conducted by Stevenson et al., in 2003 showed no significant difference in the incidence of SSIs in patients receiving antibiotics compared with a placebo.(38) In addition, the double blind RCT conducted by Aydin et al., 2010 again showed antibiotics did not significantly affect the SSI incidences in complex hand injuries. (39)

Evidence supporting the role of antibiotics in hand trauma is mixed and its validity is further compounded by a scarcity of high quality studies and small patient populations. Therefore, the aim of this study is to use the power of a NMA to update the current evidence base regarding antibiotic use in all hand trauma and support development of clear guidelines to allow evidence based antibiotic use in trauma related hand surgery.

Abbreviations

CDC centre for disease control and prevention

CI confidence interval

CINeMA Confidence in Network Meta-Analysis
GRADE Grading of Recommendations, Assessment, Development, and Evaluation

NICE National Institute for Health and Care Excellence

NMA Network meta-analysis
PRISMA Preferred Reporting Items of Systematic Reviews and Meta-Analyses for Systematic Review Protocols
PROSPERO International Prospective Register of Systematic Reviews RCT Randomized controlled trial
RoB Risk of bias

ROBINS-I Risk Of Bias In Non-Randomized Studies - of Interventions

ROB-MEN risk of bias due to missing evidence in network meta-analysis
SIDDE Separating indirect evidence from direct evidence
RCT Randomised controlled trials

RR risk ratio

SSI surgical site infection

Declarations

Ethics approval and consent to participate.

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

None known

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Authors' contributions

JW and RW supervised the study. CZ, SF, JW and RW designed the study and provided clinical and methodological advice. CZ drafted the manuscript and registered the protocol with PROSPERO. All authors critically reviewed the manuscript and approved its final version.

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Not applicable

References

1. Statistics » A&E Attendances and Emergency Admissions [Internet]. [cited 2023 Aug 16]. Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/ae-waiting-times-and-activity/
2. Manley OWG, Wormald JCR, Furniss D. The changing shape of hand trauma: an analysis of Hospital Episode Statistics in England. J Hand Surg Eur Vol. 2019 Jun;44(5):532–6.

3. O'Sullivan ME, Colville J. The economic impact of hand injuries. J Hand Surg Edinb Scotl. 1993 Jun;18(3):395–8.
4. Rosberg HE, Carlsson KS, Cederlund RI, Ramel E, Dahlin LB. Costs and outcome for serious hand and arm injuries during the first year after trauma – a prospective study. BMC Public Health. 2013 May 24;13(1):501.
5. The Economic Impact of Hand Injuries [Internet]. [cited 2023 Aug 21]. Available from: https://journals.sagepub.com/doi/epdf/10.1016/0266-7681%2893%2990072-N
6. Baldwin AJ, Jackowski A, Jamal A, Vaz J, Rodrigues JN, Tyler M, et al. Risk of surgical site infection in hand trauma, and the impact of the SARS-CoV-2 pandemic: A cohort study. J Plast Reconstr Aesthet Surg. 2021 Nov;74(11):3080–6.
7. Platt AJ, Page RE. Post-Operative Infection Following Hand Surgery: Guidelines for Antibiotic Use. J Hand Surg. 1995 Oct;20(5):685–90.
8. Dunn JC, Means KR, Desale S, Giladi AM. Antibiotic Use in Hand Surgery: Surgeon Decision Making and Adherence to Available Evidence. Hand N Y N. 2020 Jul;15(4):534–41.
9. Shapiro LM, Zhuang T, Li K, Kamal RN. The Use of Preoperative Antibiotics in Elective Soft-Tissue Procedures in the Hand: A Critical Analysis Review. [Review]. JBJS Rev. 2019;7(8):e6.
10. Kistler JM, Munn M, McEntee R, Ilyas AM. Antibiotic Prophylaxis in Clean Hand Surgery: A Prospective Cohort Analysis of Major and Minor Complications. J Hand Surg Glob Online. 2023 Apr;S2589514123000518.
11. Bäcker HC, Freibott CE, Wilbur D, Tang P, Barth R, Strauch RJ, et al. Prospective Analysis of Hand Infection Rates in Elective Soft Tissue Procedures of the Hand: The Role of Preoperative Antibiotics. Hand N Y N. 2021 Jan;16(1):81–5.
12. Murphy GRF, Gardiner MD, Glass GE, Kreis IA, Jain A, Hettiaratchy S. Meta-analysis of antibiotics for simple hand injuries requiring surgery. Br J Surg. 2016 Apr 1;103(5):487–92.
13. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods. 2012 Jun;3(2):80–97.
14. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011 Feb;64(2):163–71.
15. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015 Jun 2;162(11):777–84.
16. Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery.
17. Borchardt RA, Tzizik D. Update on surgical site infections: The new CDC guidelines. JAAPA Off J Am Acad Physician Assist. 2018 Apr;31(4):52–4.

18. Haddaway NR, Grainger MJ, Gray CT. Citationchaser: A tool for transparent and efficient forward and backward citation chasing in systematic searching. Res Synth Methods. 2022;13(4):533–45.
19. Zabaglo M, Sharman T. Postoperative Wound Infection. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Aug 14]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560533/
20. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.
21. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919.
22. Chiocchia V, Nikolakopoulou A, Higgins JPT, Page MJ, Papakonstantinou T, Cipriani A, et al. ROB-MEN: a tool to assess risk of bias due to missing evidence in network meta-analysis. BMC Med. 2021 Nov 23;19(1):304.
23. Efthimiou O, Debray TPA, van Valkenhoef G, Trelle S, Panayidou K, Moons KGM, et al. GetReal in network meta-analysis: a review of the methodology. Res Synth Methods. 2016 Sep;7(3):236–63.
24. Jagodzinski NA, Ibish S, Furniss D. Surgical site infection after hand surgery outside the operating theatre: a systematic review. J Hand Surg Eur Vol. 2017 Mar 1;42(3):289–94.
25. Davies J, Roberts T, Limb R, Mather D, Thornton D, Wade RG. Time to surgery for open hand injuries and the risk of surgical site infection: a prospective multicentre cohort study. J Hand Surg Eur Vol. 2020 Jul 1;45(6):622–8.
26. Cassell OCS, Ion L. Are antibiotics necessary in the surgical management of upper limb lacerations? Br J Plast Surg. 1997 Oct;50(7):523–9.
27. Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, et al. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. J Stat Softw. 2023 Mar 23;106:1–40.
28. Efthimiou O, Mavridis D, Debray TPA, Samara M, Belger M, Siontis GCM, et al. Combining randomized and non-randomized evidence in network meta-analysis. Stat Med. 2017 Apr 15;36(8):1210–26.
29. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015 Jul 31;15(1):58.
30. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012 Jun;3(2):98–110.
31. König J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. Stat Med. 2013 Dec 30;32(30):5414–29.
32. Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. BMC Med Res Methodol. 2013 Mar 9;13(1):35.
33. Efthimiou O, Rücker G, Schwarzer G, Higgins JPT, Egger M, Salanti G. Network meta-analysis of rare events using the Mantel-Haenszel method. Stat Med. 2019;38(16):2992–3012.

34. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Giovane CD, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLOS Med. 2020 Apr 3;17(4):e1003082.
35. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Softw. 2010;36(3).
36. Quality statement 2: Antibiotic prophylaxis | Surgical site infection | Quality standards | NICE [Internet]. NICE; 2013 [cited 2023 Sep 6]. Available from: https://www.nice.org.uk/guidance/qs49/chapter/quality-statement-2-antibiotic-prophylaxis
37. Ketonis C, Dwyer J, Ilyas AM. Timing of Debridement and Infection Rates in Open Fractures of the Hand. Hand N Y N. 2017 Mar;12(2):119–26.
38. Stevenson J, Mcnaughton G, Riley J. The use of Prophylactic Flucloxacillin in Treatment of Open Fractures of the Distal Phalanx within an Accident and Emergency Department: A Double-Blind Randomized Placebo-Controlled Trial. J Hand Surg. 2003 Oct;28(5):388–94.
39. Aydin N, Uraloğlu M, Burhanoğlu ADY, Sensöz Ö. A Prospective Trial on the Use of Antibiotics in Hand Surgery: Plast Reconstr Surg. 2010 Nov;126(5):1617–23.

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- PRISMANMAchecklist.pdf